C6 density lipoprotein.

Please cancel claims 45-47.

Remarks

Double Patenting

The double patenting issue will be addressed when the claims are otherwise allowable.

Rejection under 35 U.S.C. §112

Claims 42 and 45-47 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the application fails to support these claims. This rejection is respectfully traversed as to claim 42; claims 45-47 have been cancelled solely to facilitate prosecution.

The standard for whether or not claims are supported by the specification is not whether the subject matter is originally claimed, but whether or not the subject of the claims is described in the application sufficiently to enable one of skill in the art to make and use the claimed subject matter.

Support for the use of antibodies without detectable crossreactivity with other aplipoproteins is found, for example, at page 17, lines 22-24. These are referred to as "specific antibodies".

The claims in issue are outlined below, annotated with specific support in the specification (Note, however, that the support is merely exemplary, not exclusive):

42. A method for determining the relative ratio of LDL to HDL in a biological sample comprising

adding to the sample monoclonal antibody molecules immunoreactive with low density lipoprotein and not cross-reactive with high density lipoprotein and determining the amount of low density lipoprotein (page 40, line 30 to page 41, line 11; page 64, lines 9-31; pages 59-62, example 7);

adding to the sample monoclonal antibody molecules immunoreactive with high density lipoprotein and not cross-reactive with low density lipoprotein and determining the amount of high density lipoprotein (page 64, lines 9-35; page 62, example 8); and

determining the ratio of the amount of low density lipoprotein with the amount of high density lipoprotein (page 33, line 28 to page 34, line 22; page 39, lines 29-35; example 9, pages 64-65).

Claims 15-18, 20-23, 25, 27-30, 35-37, 42, and 45-47 were rejected under 35 U.S.C. §112 as non-enabled. This rejection is respectfully traversed as to all claims except 17 and 45-47.

Claims 15, 16, and 17

Claims 15-17 were rejected as "missing essential steps".

Claim 17 has been cancelled. Claims 15 and 16 have been amended to recite that the antibody complexes are separated either by immobilization of an antibody binding the lipoprotein-antibody complex or precipitation and centrifugation of the lipoprotein-antibody complexes, or the use of different labels on the antibodies. Support for these alternatives is found at page 38, lines 3-15, immobilized antibody; page 40, line 21 to page 42, line 2, where the

antibodies are in solution, complex, and precipitate; and page 42, lines 3-30.

"heading" type steps, in combination with the above method steps, should make clear what is done when in each of claims 15-16.

Claims 30, 41 and 42

Claim 30 has been amended to recite 'specifically immunoreactive" language.

Claim 41 now depends from claim 15.

Claim 42 has also been amended to include headings.

Rejections under 35 U.S.C. §102(b)

Claim 17 was rejected under 35 U.S.C. §102(b) as disclosed by Koren, et al., Atherosclerosis 95, 157-170 (1992) ("Koren A") or Koren, et al., Clin. Chem.33(1), 38-43 (1987) ("Koren B"). Claim 17 has been cancelled.

Claims 18, 20, 27, 28, 29 and 35 were rejected under 35 U.S.C. §102(b) as disclosed by Koren, et al., Biochemica et Biophysica Acta 876, 91-100 (1986) ("Koren AR") or Koren, et al., Biochemica et Biophysica Acta 876, 101-107 (1986) ("Koren AS"). This rejection is respectfully traversed.

Koren, et al. does describe D6, referred to in this application as a Pan B antibody, at page 25. It is specifically stated that this antibody is **not** specifically immunoreactive with a particular lipoprotein. The test for specificity is described in the application at page 17, line 22, to page 18, line 10. The D6 antibody is further distinguished in the application at page 26, lines 20-30. As stated at page 25, lines 25, "D6 MAb is an antibody with **equal binding and high affinity for**

all Apo b-containing lipoproteins" - and then goes on the cite for support the very references used by the examiner in this rejection.

Claim 18 has been amended to make this point even more clearly: that the claimed antibodies are those specifically immunoreactive with a single lipoprotein or apolipoprotein. Claim 18 has also been amended to recite that the antibodies are monoclonal or recombinant antibodies.

Calims 18, 20, 27 and 35 were also rejected under 35 U.S.C. §102(b) as disclosed by Marcel, et al., J. Lipid Res. 28(7), 768-777 (1987). This rejection is respectfully traversed.

As the examiner has noted, Marcel has identified antibodies that bind "epitopes [are] both expressess on **all** lipoproteins" (emphasis added). Therefore these antibodies do not bind with the required specificity.

Rejections under 35 U.S.C. §103

Claims 18, 20, 23, 25, 27, 28, 29, 30 and 35 were rejected under 35 U.S.C. §103 as obvoius over Koren, et al., Biochemica et Biophysica Acta 876, 91-100 (1986) ("Koren AR") or Koren, et al., Biochemica et Biophysica Acta 876, 101-107 (1986) ("Koren AS") in combination with Koren, et al., Atherosclerosis 95, 157-170 (1992) ("Koren A"). Claims 18, 20, 23, 25, 27, 28, 29, 30 and 35 were also rejected under §103 as obvious over marcell, in combination with Koren A. These rejections are respectfully traversed.

As discussed above, neither Koren AR nor Koren AS described an antibody which is sepcifically immunoreactive with a single apolipoprotein or lipoprotein, to a lipid and

conformation independent epitope.

Koren A fails to make up for this deficiency.

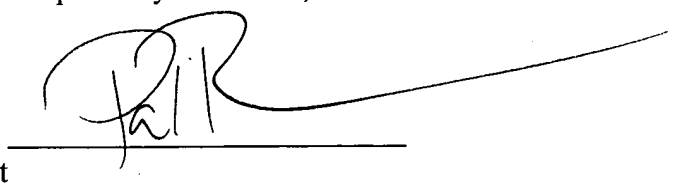
As discussed above, Marcel describes antibodies which are reactive with multiple apolipoproteins or lipoproteins.

Until applicants described a method to make an antibody as claimed, no one had ever produced and identified an antibody that was specifically immunoreactive with a single apolipoprotein or lipoprotein, at a lipid and conformation independent epitope.

Therefore, even in combination, the claimed composition cannot be obvious.

Allowance of all claims 15-16, 18, 20-23, 25, 27-37, 41, and 42, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,



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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: February 22, 1999

Appendix: Claims as Amended

15. (three times amended) A method for determining the relative ratio of VLDL to HDL in a biological sample comprising

determining the amount of VLDL in the sample by

determining the amount of Apo C-III present in the VLDL in the sample by

providing Pan B antibody which is characterized by an equal binding and high affinity for all Apo B-containing lipoproteins in human plasma,

providing monoclonal antibody immunoreactive with Apo C-III,

contacting the antibody reactive with Apo C-III with the biological sample to form complexes between the antibody and the Apo C-III containing lipoprotein particles,

contacting the Pan B antibody with the biological sample,

separating the complexed antibody-lipoprotein particles from the biological sample, and

determining the amount of Apo C-III associated with Apo B, which is the amount of Apo C-III present in VLDL in the sample; and

determining the amount of HDL in the sample by

determining the amount of Apo C-III present in the HDL in the sample by

providing Apo A-I monoclonal antibody immunoreactive specifically with Apo A-I,

providing monoclonal antibody immunoreactive with Apo C-III,

contacting the antibody reactive with Apo C-III with the biological sample to form complexes between the antibody and the Apo C-III containing lipoprotein particles,

contacting the anti-Apo A-I antibody with the biological sample,

separating the complexed antibody-lipoprotein particles from the biological sample,

determining the amount of Apo C-III associated with Apo A-I, which is the amount of Apo C-III present in HDL in the sample, and

determining the ratio of Apo C-III present in VLDL in the sample and Apo C-III present in HDL in the sample which is the ratio of VLDL to HDL,

wherein the VLDL and HDL are measured in the same sample using immobilized antibodies or measured by immunoprecipitation in separate samples.

16. (three times amended) A method for determining the relative ratio of VLDL to HDL comprising

determining the amount of VLDL in the sample by

determining the amount of Apo E present in the VLDL in the sample by

providing Pan B antibody which is characterized by an equal binding and high affinity for all Apo B-containing lipoproteins in human plasma,

providing monoclonal antibody which binds to Apo E associated predominantly with VLDL,

contacting the antibodies reactive with Apo E associated with VLDL with the biological sample to form complexes between the antibodies and Apo E containing particles,

[separating the complexed antibody-ApoE containing particles from the biological sample,]

contacting Pan B antibody with the biological sample, and

determining the amount of Apo E associated with Apo B which is the Apo E present predominantly in VLDL in the sample;

removing the complexed anti-Apo E:Pan B:Apo E containing particles by immobilization of the anti-Apo E antibodies or centrifugation of complexed particles;

and

determining the amount of HDL in the sample by

determining the amount of Apo E present in the HDL in the sample by

providing Apo A-I monoclonal antibody immunoreactive specifically with Apo A-I,

providing monoclonal antibody which binds to Apo E predominantly associated with HDL,

contacting the antibodies reactive with Apo E to the biological sample to form complexes between the antibodies and Apo E containing particles,

[separating the complexed antibody-ApoE containing particles from the biological sample,]

contacting Pan B antibody with the biological sample,

determining the amount of Apo E associated with Apo A-I, which is the amount of Apo E present in HDL in the sample, and

determining the ratio of Apo E present in VLDL in the sample and Apo E present in HDL in the sample which is the ratio of VLDL to HDL.

Please cancel claim 17.

18. (three times amended) A composition for determining the concentration of a lipoprotein, apolipoprotein, or lipid associated with a single specific lipoprotein in a biological sample comprising:

monoclonal or recombinant antibody molecules specifically immunoreactive with a single specific lipoprotein or apolipoprotein, wherein the antibody molecules are selected from the group consisting of monoclonal antibodies, recombinant antibodies, and monoclonal antibody fragments that specifically bind to a stable, conformation independent epitope which is uninfluenced by the lipid content of the lipoprotein, apolipoprotein, or lipid associated with a specific lipoprotein.

20. (amended) The composition of claim 18 wherein the antibodies are monoclonal antibodies.

21. The composition of claim 18 wherein the antibody is the anti-LDL monoclonal antibody produced by the hybridoma cell line HB_3cB_3 ATCC designation number HB 11612.

22. The composition of claim 18 wherein the antibody is a recombinant anti-LDL $RcB_3M_1D_4$ ATCC designation number 69602.

23. (twice amended) The composition of claim 18 further comprising a second monoclonal antibody immunoreactive with a second distinct epitope of the lipoprotein or

apolipoprotein which is immunoreactive with the first antibody.

25. (amended) The composition of claim further comprising at least one internal standard comprising a known amount of a particular lipoprotein, lipoprotein lipid, or apolipoprotein.

27. The composition of claim 18 wherein the apolipoprotein is selected from the group consisting of Apo A-I, Apo A-II, Apo B, Apo C-III, and Apo E.

28. (twice amended) The composition of claim 18 for determining the relative ratio of VLDL to HDL further comprising

Pan B antibody which is characterized by an equal binding and high affinity for all Apo B-containing lipoproteins in human plasma,

monoclonal antibody specifically immunoreactive with Apo C-III, and

monoclonal Apo A-I antibody immunoreactive specifically with Apo A-I.

29. (twice amended) The composition of claim 18 for determining the relative ratio of VLDL to HDL further comprising

Pan B antibody which is characterized by an equal binding and high affinity for all Apo B-containing lipoproteins in human plasma,

monoclonal antibody which predominantly binds to Apo E associated with VLDL ,

monoclonal Apo A-I antibody immunoreactive specifically with Apo A-I, and

monoclonal antibody which predominantly binds to Apo E in HDL.

30. (three times amended) The composition of claim 18 for determining the relative ratio of LPA-I and LPA-II lipoprotein particles comprising

monoclonal Apo-A-I antibody [which binds] <u>specifically immunoreactive with</u> Apo A-I lipoproteins in human plasma; and

monoclonal Apo A-II antibody <u>specifically</u> immunoreactive [specifically] with Apo A-II.

35. An antibody molecule specifically immunoreactive with LDL that does not significantly cross-react with other lipoproteins in whole blood, blood plasma or blood serum, wherein the molecule is selected from the group consisting of monoclonal antibodies, recombinant antibodies, and fragments thereof and wherein the antibody specifically binds to a stable, conformation independent epitope which is uninfluenced by the lipid content.

36. The antibody molecule of claim 35 wherein the antibody is the anti-LDL monoclonal antibody produced by the hybridoma cell line HB_3cB_3 ATCC designation number HB 11612.

37. The antibody molecule of claim 35 wherein the antibody is a recombinant anti-LDL $RcB_3M_1D_4$ ATCC designation number 69602.

41. (amended) The method of claim [12] <u>15</u> wherein binding of the second antibody forms a precipitate of the [antigen and both bound antibodies] <u>antibody:lipoprotein complex</u> which can be detected in a solution.

42. (amended) A method for determining the relative ratio of LDL to HDL in a biological sample comprising

<u>determining the amount of LDL in the sample by</u>

adding to the sample monoclonal antibody molecules immunoreactive with low density lipoprotein and not cross-reactive with high density lipoprotein and determining the amount of low density lipoprotein;

determining the amount of HDL in the sample by

adding to the sample monoclonal antibody molecules immunoreactive with high density lipoprotein and not cross-reactive with low density lipoprotein and determining the amount of high density lipoprotein; and

determining the ratio of the amount of low density lipoprotein with the amount of high density lipoprotein.

Please cancel claims 45-47.